INFECTIONS ASSOCIATED WITH UREMIA AND DIALYSIS

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INTRODUCTION

Over 60,000 people in the United States develop end-stage renal disease (ESRD) with an annual expected increase of 6% to 9%. Dialysis is the mainstay of treatment and according to the United States Renal Data System (USRDS) 1997 report, more than 200,000 people were receiving either hemodialysis or peritoneal dialysis with nearly 1 of every 1000 people on dialysis.[119]

Uremia is associated with an increased susceptibility to infections and until recently the pathophysiology has been understood poorly. Infections remain a major cause of morbidity and mortality in patients with uremia and ESRD. Most of these infections are of bacterial origin and account for the majority of hospitalizations in this patient population.[86, 96] Infections were responsible for 12 to 22% of deaths among dialysis patients in the United States and Canada. Infections are the second most common cause of mortality in patients on dialysis, after coronary artery disease.[119]

The presence of a substantial impairment of immunity in patients with uremia has been well documented.[31, 34] Vascular access sites and peritoneal dialysis (PD) catheters serve as ready portals of entry for pathogens. Chronic renal failure (CRF) and the subsequent need for maintenance hemodialysis (HD) can alter neutrophil function, reduce the ability for phagocytosis, depress natural killer cell activity, and can alter T and B cell function.[3, 18, 23, 32, 48, 50, 51, 78, 87, 120] A profound leukopenia occurs from complement activation induced by the interaction with the

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dialyzer membrane.[56,77] These functional and quantitative abnormalities of cellular function account for the increased susceptibility to infection, and are independent of the cause of uremia or ESRD. The host defense defects in uremia are the following:

- Depressed neutrophil (PMN) function
- Leukopenia secondary to complement activation
- Impaired phagocytosis
- Reduced natural killer (NK) cell activity
- Decreased T and B lymphocyte function
- Decreased T lymphocyte response to standard antigens

Various factors contribute to the altered cellular function in uremia. These include low albumin from malnutrition, metabolic acidosis, increased intracellular calcium, low molecular weight uremic toxins, and the presence of circulating inhibitors to chemotactic factors.[49,121] Iron overload can impair immune function, enhances bacterial growth and virulence and thereby predisposes to an increased risk of infection in uremic patients.[114] Predisposing factors to infection in uremic/dialysis patients are the following:

- Low albumin secondary to malnutrition
- Increased intracellular calcium
- Iron overload
- Low molecular weight uremic toxins
- Metabolic acidosis
- Circulating inhibitors to chemotactic factors
- Decreased production of endogenous pyrogens
- Invasive vascular procedures for dialysis access

Decreased production of endogenous pyrogens may cause a delay in recognition of infection.[79] Skin test responses to standard antigens are impaired markedly in uremic patients. With the advent of dialysis for uremia, patients are subject to invasive procedures such as placement of intravenous catheters for temporary and permanent dialysis, that pose an increased risk of infections and for the same reasons dialysis patients are at increased risk of infections by resistant organisms.[86]

SKIN AND BONE INFECTIONS

Chronic uremia secondary to diabetic nephropathy accounts for about 25 percent of new patients treated by maintenance hemodialysis. Cellulitis is more frequent in patients with ESRD who are diabetics and have peripheral neuropathy or peripheral vascular disease. Repeated skin punctures associated with dialysis access increase risk for skin and soft tissue infections. Abscess formation at the puncture site of the fistula can occur and is usually caused by *Staphylococcus aureus*. Aggressive measures should be undertaken and the duration of treatment in these patients is often more prolonged than for nondialysis patients.

Osteomyelitis may occur as a complication in patients on HD. The access for HD acts as a portal of entry for the spread of hematogenous infection. Osteomyelitis usually occurs within 24 to 60 months after initiation of HD, and the most common sites involved are the ribs and thoracic vertebrae. *Staphylococcus aureus* is the usual isolate. Of importance is the difficulty in diagnosing this condition as the clinical signs and radiographs may mimic those of renal osteodystrophy.[74] Treatment is empiric and is modified based upon the cultures when available. Osteomyelitis may also occur as a direct extension of cellulitis especially in diabetics. Spinal epidural abscess, a rare infection, is secondary to access site in this patient population and the major isolate is *S. aureus*.[97]

ACCESS SITE–ASSOCIATED BACTEREMIAS

Despite the advances in design and technique in placement of catheter for access for HD, infection remains a major cause of morbidity and mortality.[1] The access for dialysis can be temporary with an indwelling catheter, or permanent with placement of an arteriovenous fistula (AVF) or a synthetic vascular graft (VG). Tunneled, cuffed Silastic catheters have emerged as the preferred access for temporary use. Indwelling catheters pose a far greater risk of bacteremia compared to an AVF or a graft. Bacteremia results from migration of bacteria from the skin or contamination of the catheter lumen.[24]

The incidence of bacteremia varies with the site and duration of the catheter, and infection is the principal reason for removal of the catheter. The bacteremia rate has been reported to be 1.6 to 7.7 bacteremias per 1000 catheter days with the temporary dialysis catheters and 0.2 to 0.5 bacteremias per 1000 catheter days with the tunneled, cuffed catheters.[24,69] Various studies comparing the incidence of infections between AVF and vascular grafts have found higher rates with the later type of vascular access.[10,67,128] A high rate of catheter related bacteremia is associated with femoral or internal jugular vein placement of a catheter compared to the subclavian vein.[62] The probability of access site infection during the first year of hemodialyis is about 20% with a VG and about 30% with a peritoneal dialysis catheter.[21]

S. aureus remains the most common cause of vascular site–associated bacteremia in patients on HD accounting for over half of HD catheter related infections.[65,96] Enterococci and aerobic gram-negative bacilli are responsible for the remainder. Although methicillin-resistant *Staphylococcus aureus* (MRSA) causes the same spectrum of vascular access site infections as methicillin sensitive *S. aureus* (MSSA), MRSA causes less than 10% of vascular access site infections in HD patients. Exit site infection (ESI) and catheter associated bacteremia require an empiric antimicrobial regimen that includes a broad spectrum coverage for both gram-positive and gram-negative organisms. Treatment should be modified to a regimen that is more appropriate for the pathogen, when

culture results are obtained. In cases of catheter associated bacteremias, catheter should be removed whenever possible. In the absence of an alternate site for vascular access, catheter salvage can be attempted. Catheter removal may be life saving in patients who continue to have persistent fevers, positive blood cultures or becomes hemodynamically unstable.

Patients on dialysis have an increased rate of S. aureus nasal colonization and are an important risk factor in S. aureus infections.[20] Elimination of staphylococcal nasal carriage has been found to reduce the incidence of infection in patients on dialysis.[68] Various strategies to decrease the S. aureus nasal carriage have been compared.[54] Injudicious use of nasal mupirocin often is accompanied by a subsequent high level of S. aureus resistance. The most effective way to treat patients with positive nasal cultures is with topical nasal mupirocin application twice a day for 5 days, which has enhanced the quality of life in HD patients. In patients on PD, elimination of nasal carriage decreased the ESI rate, but the effect on the incidence of peritonitis is unclear.

Endocarditis, epidural abscess, recurrent bacteremias, and septic arthritis are potential complications secondary to catheter associated bacteremia. Patients who remain febrile or have persistent positive cultures after removal of the catheter should undergo a thorough evaluation to find a distant source.

Vancomycin Resistant Enterococci

Most strains of Enterococcus faecium are vancomycin resistant and are termed vancomycin resistant enterococci (VRE). The emergence of VRE was primarily seen in patients in the intensive care units but VRE is now encountered with increasing frequency in patients outside the intensive care units. Most patients with positive VRE cultures are colonized with rather than infected with Enterococcus faecium. The widespread use of vancomycin in dialysis patients and the convenience of infrequent dosing of vancomycin in hemodialysis patients has led to the emergence of VRE. The emergence of VRE and an increasing incidence of colonization with VRE can be a potential source of serious infection. Severely ill patients who previously have received extensive antibiotic therapy are at risk for VRE bacteremia and dialysis patients with recurrent infections and frequent hospitalizations are no exception. Patients receiving outpatient PD are at a low risk for acquiring VRE because these patients receive less intravenous vancomycin than HD patients.[93] There is no correlation with the duration of dialysis and the presence of VRE, nor is there an increased risk of mortality in VRE positive patients.[107] There is a correlation in HD patients of intravenous vancomycin use and subsequent VRE colonization.[44] Dialysis patients with VRE colonization should be placed on precautions but not treated.[16] Patients

infected with VRE may be treated with chloramphenicol, doxycycline, or linezolid.

SEPTIC SHOCK

Septicemia is one of the most serious infections in dialysis patients and accounts for about three fourths of deaths caused by infections.[19] Over a 7-year follow-up of dialysis patients Powe et al reported at least one episode of septicemia in 11.7% of HD patients and in 9.3% of PD patients.[103] Churchill et al in the Canadian Hemodialysis Morbidity study reported similar findings on the incidence of septicemia.[22] Immune deficiency associated with uremia, malnutrition, and old age that further impairs the immune response and the presence of comorbid conditions such as diabetes mellitus increases the risk of septicemia. In addition a regular disruption of the skin barrier to gain access for dialysis puts these patients at significant risk for septicemia. The type of vascular access for hemodialysis also influences the incidence of septicemia: a 50% higher risk is associated with a temporary catheter over a native fistula, and a 33% higher risk with a Gortex graft over a native fistula. In hemodialysis and peritoneal dialysis patients, old age and the presence of diabetes mellitus was associated with a higher risk of septicemia.

In hemodialysis patients the major potential sources of septicemia were vascular access and internal prostheses related infection (26%), decubitus ulcers (6%), urinary tract infections (5%), and nosocomial pneumonia (5%). Others include gangrene (3%), endocarditis (2%), and abscess of foot (1%). The major potential source of bacteremia in peritoneal dialysis patients was catheter related infection (12%) followed by pneumonia (12%), urinary tract infections (8%), peritonitis (5%), endocarditis (2%), and cellulitis and abscess of foot (2%).[103]

Staphylococcus spp. remain the predominant organisms associated with septicemic episodes caused by vascular site infections.[35] Pseudomonas septicemia secondary to inadequate mixing of the disinfectant with the tap water has been reported in a dialysis unit reusing capillary dialyzers. Contamination of the dialyzers has been implicated in cases of gram-negative bacteremia in outpatient hemodialysis units.

Outbreaks of fatal Salmonella enteritidis septicemia in uremic patients have been described. Mortality with S. enteritidis is low, but the high mortality in this patient population is probably related to the impaired immune response associated in uremia.[80]

CENTRAL NERVOUS SYSTEM INFECTIONS

The incidence of meningitis among patients with uremia or on dialysis is not known. Meningitis and other infections of the central nervous system should be considered in dialysis patients with fever, headache, neck stiffness, or other symptoms or signs pertaining to the

central nervous system. Streptococcal meningitis has been reported as a complication of peritonitis in a patient on PD.[81] In a normal adult host, Escherichia coli bacteremias are common but meningitis is rare. In patients with uremia, fatal E. coli meningitis has been reported.[6] Cryptococcal peritonitis from peritoneal dialysis with subsequent meningitis has been described.[112] Listeria meningitis although rare, should be kept in mind in patients undergoing hemodialysis.[12]

Mucormycosis, a life threatening fungal infection, is characterized by sinusitis with rapid invasion to adjacent structures, including the central nervous system. There is a significant risk of mucormycosis in diabetics and in hemodialysis patients treated with deferoxamine as a form of aluminum chelation therapy.[9, 63, 109] Rhinocerebral and disseminated disease is the most common presentation of mucormycosis.

A rare case of metastatic endophthalmitis caused by Serratia marcescens presumably from an infected dialysis catheter has been reported.[83]

CARDIOVASCULAR INFECTIONS

Infectious endocarditis (IE) has been reported as a secondary consequence of intravascular access infections in patients on hemodialysis or peritoneal dialysis.[71, 105] A high index of suspicion is imperative on the part of the clinician, as the usual signs of infection such as fever or leukocytosis may be absent or obscured in renal failure. Some of the classic features of IE (e.g., hematuria, heart murmur, and anemia) can occur as a result of the renal disease, giving rise to difficulties in diagnosis. IE should be suspected in dialysis patients with persistent bacteremia, changing heart murmur, and embolic phenomena. The incidence of bacterial endocarditis has varied from 2% to 5% in regularly dialyzed patients.[25]

There is an increased probability of IE with access associated bacteremia occurring more commonly 1 to 2 years after initiation of hemodialysis.[73] In hemodialysis patients IE has a high mortality and is seen more frequently with synthetic VG and venous catheters than with native AVF.[84] Usually IE involves a single valve with aortic and mitral valve being more common. Right-sided endocarditis is associated with the presence of subclavian dialysis catheters, and quadri-valvular endocarditis involving the four valves has been reported.[57, 100] The usual causative organisms include S. aureus and Staphylococcus epidermidis along with Enterococcus and Streptococcus viridans.[106]

PULMONARY INFECTIONS

There appears to be no increased susceptibility to respiratory tract infections in patients with ESRD, compared with the general population, but infections of the upper and lower respiratory tract are the second leading cause of infection-related deaths among patients on dialysis.[119]

Community acquired pneumonia, though not more common compared with the general population, may present diagnostic difficulties caused by fluctuation of pulmonary fluid shifts associated with renal failure and dialysis. Treatment should be started if there is a high index of suspicion, pending diagnostic test results.

Pulmonary Tuberculosis

Because of impaired cellular immunity, patients in chronic renal failure have an increased risk of pulmonary tuberculosis.[2] The risk of tuberculosis is particularly high within the first year on dialysis. Data from population based studies show that patients on dialysis have a 25.3 relative risk of acquiring pulmonary tuberculosis when compared to age matched controls in the general population.[19] In patients who are on dialysis there is an increased reactivation of old pulmonary tuberculosis. In addition, various studies have documented a predominance of extrapulmonary tuberculosis. Patients who are being started on dialysis should have purified protein derivative (PPD) skin tests done. It is important that patients with a positive PPD response be placed on chemoprophylaxis. There is a high prevalence of anergy in dialysis patients, which accounts for the high rate of false, negative PPD skin tests seen in this patient population.[11, 126] Additional clinical testing to confirm the diagnosis is needed in these patients. Treatment of pulmonary tuberculosis in patients with ESRD does not differ from the general population.

GASTROINTESTINAL INFECTIONS

Peritonitis Secondary to Peritoneal Dialysis

Over the last two decades peritoneal dialysis has become a common alternative to hemodialysis in the treatment of chronic renal failure. The prevalence rate of peritonitis is 1 to 1.5 episodes per patient per year, and peritonitis is the most common reason for hospitalization in this patient population.[95] In recent years the incidence of peritonitis has decreased but it still remains the most common reason for discontinuation of PD.[8]

Incidence of peritonitis varies among different centers and with the method of peritoneal dialysis. The risk of developing peritonitis is directly proportional to the length of dialysis: 60% by the end of one year of treatment, 80% by two years and 90% by three years.[102, 108] A major route of spread of infection is as a consequence of intraluminal contamination that is associated with frequent manipulations of the catheter.[94] Failure to comply with the standard recommendations for catheter care is associated with an increased incidence of infection. Patients on chronic ambulatory peritoneal dialysis (CAPD) have the highest risk of devel-

oping peritonitis compared to patients on chronic intermittent peritoneal dialysis (CIPD). Patients on continuous cycling peritoneal dialysis (CCPD) develop peritonitis at rates intermediate between those described for CAPD and CIPD.

Peritonitis in CAPD patients is characterized by abdominal pain, tenderness, and cloudy peritoneal effluent with greater than 100 neutrophils/mm,[3] and the presence of microorganisms in the peritoneal fluid. Gram-positive organisms account for two thirds of all episodes of peritonitis.[4] S. epidermidis is the most common and S. aureus is the next most common isolate (Table 1). Nonenterococcal streptococci and enterococci are less common but account for a significant number of episodes. E. coli and other Enterobacteriaceae are the most prevalent gram-negative organisms. Pseudomonas aeruginosa isolates account for a few episodes and anaerobes are rarely if ever isolated. The presence of anaerobes or a polymicrobial isolate raises the possibility of peritonitis secondary to a bowel perforation. Bowel perforation can be secondary to a visceral leakage from ischemic bowel disease, diverticulitis, or perforation of a viscus and necessitates switching from peritoneal dialysis to hemodialysis.

Fungal peritonitis has become relatively common with the improvement in therapy for bacterial peritonitis. Prior hospitalization, recent episodes of bacterial peritonitis, and treatment with antibiotics all predispose to the development of fungal peritonitis. It is difficult to clinically

Table 1. PATHOGENS CAUSING PERITONITIS IN CHRONIC AMBULATORY PERITONEAL DIALYSIS PATIENTS

Common	Rare
Bacteria	**Fungi**
Staphylococcus aureus	Candida guilliermondii
Staphylococcus epidermidis	Candida parapsilosis
(coagulase-negative staphylococci)	Candida tropicalis
Enterobacter	Alternaria
Klebsiella pneumoniae	Penicillium
Escherichia coli	Fusarium
Nonenterococcal streptococci	Rhodotorula rubra
Enterococci	**Mycobacteria**
Fungi	Mycobacterium fortuitum
Candida albicans	Mycobacterium chelonei
Nonpathogens	Mycobacterium tuberculosis
Bacteroides fragilis	
Uncommon	
Bacteria	
Acinetobacter	
Alcaligenes	
Aeromonas	
Achromobacter	
Flavobacterium	
Proteus	
Pseudomonas aeruginosa	

differentiate fungal peritonitis from bacterial peritonitis except by Gram stain and culture of the dialysate. The most common fungal isolate is Candida albicans followed by other Candida species.[36,66]

Less commonly isolated microorganisms include Mycobacterium spp, Pasteurella multocida and Xanthomonas maltophila.[7,39,52,91,111,115] Tuberculous peritonitis is a major problem in endemic areas and in high risk groups. Confirmation of the tuberculous peritonitis is based on cultures and treatment consists in initiating antituberculous regimen and removal of the peritoneal catheter.[104] Although rare, Listeria monocytogenes peritonitis has been described in CAPD patients.[82] Aseptic or culture negative peritonitis is a common entity but viral or parasitic causes of peritonitis are uncommon and should be considered in patients with culture negative peritonitis.[76,122]

Peritonitis secondary to appendicitis, cholecystitis, pancreatitis, or from a perforated viscus may mimic peritonitis secondary to peritoneal dialysis and this should be kept in mind in this patient population. The outcome of peritonitis with gram-positive organisms is worse with S. aureus, and the poor outcome with gram-negatives is independent of Pseudomonas or polymicrobial involvement.[11]

Peritoneal Catheter Exit Site Infections

With the decline in the incidence of peritonitis because of new innovations in PD, there has been a proportional increase in the incidence of exit site infections (ESIs). Bacterial colonization most often occurs soon after placement of the peritoneal dialysis catheter and staphylococcus may secrete a biofilm/slime layer (glycocalyx), which enhances further bacterial growth and acts as a barrier to antimicrobial agents. Patients who develop an infection early in their dialysis history tend to be more prone to subsequent infections. The incidence of ESI is directly proportional to the size of the exit wound. S. aureus by far remains the predominant organism colonizing the exit site and accounts for greater than 50% of ESIs. Less frequent are S. epidermidis (20%), Pseudomonas aeruginosa (8%), and E. coli (4%). It has been well documented that patients who are nasal carriers of S. aureus are at increased risk of infection and are prone to recurrent infection.[72,101,113]

ESI is suggested by the presence of pain, erythema, tenderness, skin induration, or purulent discharge from the exit site. ESI may progress from a mild infection to abscess formation and tunnel infection, but the demarcation may not be clinically obvious. Identification of positive cultures from the exit site in the absence of inflammation indicates colonization but not infection. Early recognition and prompt therapy is important for a successful outcome. Ultrasonography is useful in the early diagnosis of tunnel infections and in assessing the prognosis. Recommendations have been made for removal of the catheter in patients with no evidence of sonographic improvement after 2 weeks of antibiotic therapy.[123] Treatment of ESI is empiric based upon the

predominant organisms (e.g., staphylococci) that may be modified subsequently when the culture results are available.

Fungal ESIs are rare compared to fungal peritonitis secondary to peritoneal dialysis. It is important to rule out contamination, but with a definite fungal ESI the catheter should be removed. Ultrasonography, CT scanning, or gallium scan may demonstrate the presence of an abscess in patients with no improvement after 2 weeks of antibiotic therapy. Catheter removal is indicated with resistant infection, fungal peritonitis or abscess, or a fungal ESI.

The Mupirocin Study Group reported that there is a lower incidence of persistent nasal carriage of *S. aureus* and a decreased incidence of ESIs caused by *S. aureus* in patients treated with mupirocin nasal ointment twice daily for 5 days every 4 weeks.[89]

Clostridium difficile

Various studies have described an increased incidence of *Clostridium difficile* in uremic patients and are associated with a severe course.[5,75] Cunney et al showed that the incidence of *C. difficile* diarrhea was 10.7 per 1000 admissions for chronic renal failure patients compared with 2.7 per 1000 admissions among patients without renal failure.[28] Advanced age, poor nutrition, antimicrobial therapy, impaired host defenses, intestinal motility, and arteriosclerosis with ischemia involving the gut are the common risk factors in patients with uremia. Frequent hospitalizations and subsequent cross infection is a major contributing factor. Antimicrobial therapy particularly due to β-lactams or clindamycin is the major risk factor predisposing to *C. difficile* diarrhea.[85] The presentation of symptoms and signs and management of *C. difficile* infection is similar to the regimen used in patients without renal failure and patients not on dialysis.

Gastroenteritis

There is no known increased incidence of viral gastroenteritis in uremic patients than in the general population. Because of the immunosuppression, patients may have a decreased resistance to enteric viral pathogens. Careful attention must be given to issues of gastrointestinal fluid loss with dialysis therapy, and the impact on the effective circulating volume. Antidiarrheal agents such as loperamide provide symptomatic relief.

Diverticulitis

In patients with renal failure or on dialysis therapy the presentation of diverticulitis may be more insidious than in the general population.

Patients with polycystic kidney disease tend to have an increased association of diverticula and therefore patients with ESRD secondary to polycystic disease may have an increased incidence of diverticulitis. The modalities of treatment in this patient population do not differ from patients without renal failure.

Helicobacter pylori

There is a great variation in the literature with regard to the prevalence of *Helicobacter pylori* infection in ESRD patients, which appears to be similar to or even lower than that of the general population. When compared to age matched, sex matched controls, immunosuppression in patients with uremia does not seem to predispose them to higher colonization rates with *H. pylori*.[29,45] There is a poor correlation between endoscopic and histologic changes and bacteriological studies in ESRD patients.[88,124]

GENITOURINARY TRACT INFECTIONS

Urinary Tract Infection

In ESRD patients on hemodialysis the urinary tract is often a reservoir for infection.[17] Urinary tract infections (UTIs) are more prevalent among patients with renal failure. Urinary bladder catheterization is the most frequent predisposing factor. UTIs per se do not appear to have a major impact on the outcome of ESRD but may act as a portal of entry for organisms causing bacteremia. Bacterial infections are one of the most common infectious complications occurring among patients with acute and chronic renal failure. The spectrum of organisms causing UTIs in uremic patients does not differ significantly from those in the normal population and the usual isolates are *E. coli*, and other Enterobacteriaceae, *Enterococcus*, *Pseudomaonas aeruginosa*, and *Candida*.

There are conflicting views about the significance of pyuria (>10 white blood cells/high power field) in asymptomatic dialysis patients. Chaudhry et al found an increased propensity for UTIs in patients with pyuria while Eisinger et al found a poor correlation between pyuria and UTI.[17,37] Hence the diagnosis of a UTI in the presence of pyuria in an asymptomatic dialysis patient rests upon the presence of a positive urine culture.

Chronic renal failure and hemodialysis are important risk factors for fungal UTIs. Other risk factors in dialysis patients comprise diabetes mellitus, higher age, and prolonged and extensive use of broad spectrum antibiotics that predispose to upper tract or systemic fungal infections.[70] *C. albicans* is the major species but non-*albicans Candida* species account for a large number of fungal UTIs.

Collection of pus in a nonfunctioning urinary bladder can be an

overlooked cause of fever in anuric dialysis patients. Treatment depends upon the condition of the patient and the results of the culture which often show multiple organisms. Management of symptomatic UTIs in patients with renal failure and on dialysis does not differ significantly from patients without renal failure.

VIRAL HEPATITIS

Hemodialysis patients are at an increased risk of developing liver disease caused by blood-borne viruses, with hepatitis C virus (HCV) being the most common viral infection in these patients.

Hepatitis B

Hepatitis B (HBV) is a significant cause of morbidity and mortality in hemodialysis patients and fortunately the incidence in this patient population is on the decline.[40] This is owing to rigorous infection control strategies; routine screening of patients and staff for hepatitis B virus surface antigen (HBsAg), vaccination of susceptible patients and staff, use of dedicated machines, and prohibition of dialyzer reuse in HBsAG positive patients.[58,90]

Hepatitis C

The incidence and prevalence of anti-HCV among patients on dialysis vary widely in different countries but is consistently higher than in the general population.[30,99] HCV infection is endemic among patients on dialysis. In the United States the prevalence of anti-HCV was 10.4% (range 0% to 64%) among patients from the dialysis centers that participated in the National Surveillance of Dialysis associated Diseases.[116,117] Fortunately the incidence and prevalence of HCV among patients on dialysis are declining. In the United States the incidence of HCV declined from 1.7% in 1982 to 0.3% in 1995.[116] A similar decline in the prevalence of anti-HCV in dialysis patients has been reported from among the member nations of the European Dialysis and Transplant Association. This decline is because of the advent of screening of blood products for anti-HCV and the initiation of infection control measures in the dialysis units. There is still a risk of acquiring HCV infection by nosocomial transmission within the dialysis units and the 0.4% to 1.5% incidence of anti-HCV is a cause for concern.[99]

The major risk factors for HCV infection are the duration of ESRD, the mode of dialysis, and the prevalence of HCV infection in the dialysis unit. Patients on peritoneal dialysis are at lower risk for HCV infection with lower rates of seroconversion being reported for patients on peritoneal dialysis compared to patients on hemodialysis.[15] Though there are

arguments for and against patient isolation, use of dedicated machines and a ban on dialyzer reuse, the CDC does not mandate such measures. However, rigorous infection control measures are warranted.[117]

Liver biopsy remains the only reliable method of confirming the presence and assessing the severity of liver disease in dialysis patients with HCV infection. The impact of HCV on the longevity of this patient population is unclear. The recommended therapy for patients with chronic HCV infection in the absence of renal failure consists of interferon alfa in combination with ribavirin. Because of impaired clearance in patients with renal failure, ribavirin is not recommended in this patient population. The role of interferon alfa in the treatment of HCV infection is promising, but needs to be confirmed in larger prospective trials. There is a strong correlation between higher doses and longer duration of treatment with interferon alfa and higher response rates in hemodialysis patients. However, such regimens frequently cause more adverse effects.[33,59]

Hepatitis G

Hepatitis G virus (HGV) is a new RNA virus of the Flaviviridae family and its prevalence in patients on dialysis varies widely between 3% and 57%.[16] The significance of infection with HGV in dialysis patients remains unclear but it may serve as a marker for unrecognized parenteral exposure, suggesting the need for strict adherence to universal precautions in this patient population.[41,42]

Transfusion Transmitted Virus

Coinfection with a transfusion-transmitted DNA virus (TTV) has been reported as a frequent occurrence in HCV carriers undergoing dialysis, but the clinical significance of the TTV infection is unclear.[127]

VIRUSES WITH HEPATIC INVOLVEMENT

Cytomegalovirus

Cytomegalovirus (CMV) infection should be considered in dialysis patients who have elevated transaminases in the absence of a positive serology for the hepatitis viruses. Blood products from seropositive donors transmit CMV, and screening of blood products has been effective in preventing transmission in dialysis units. There is an increased prevalence of CMV antibodies in chronic renal failure patients undergoing hemodialysis and may be because of an asymptomatic reactivation of a latent infection. Primary CMV infections are relatively uncommon in dialysis patients.[53,64,92,110]

Epstein-Barr Virus

Reactivation of Epstein-Barr virus (EBV) infection is a common finding in immunocompromised patients and may occur in patients with uremia also. Winkelspecht et al reported that there was a significant EBV reactivation in dialysis patients compared to healthy controls. Patients on hemodialysis had a higher prevalence of EBV reactivation (25%) compared to patients on peritoneal dialysis (11%) and healthy controls (6%).[125]

HUMAN IMMUNODEFICIENCY VIRUS

Patients with human immunodeficiency virus (HIV) on dialysis can be a potential source of transmission of the virus to other patients or staff in the dialysis unit. This is true of hemodialysis and peritoneal dialysis and is because of the infectious nature of the patient's blood and the peritoneal fluid. HIV transmission is highly unlikely in dialysis units that comply with standard infection control measures. The Centers for Disease Control and Prevention (CDC) does not recommend routine isolation or dedicated dialysis machines for HIV infected patients.[90]

DIAGNOSTIC APPROACH TO FEVER IN THE HEMODIALYSIS UNIT

Intermittent Fevers with Normal Serum Transaminases

Infectious disease consultation often is requested when patients on dialysis have unexplained febrile episodes. Clinically, patients with fever on dialysis usually present with intermittent unexplained fever spikes or persistent low-grade fevers usually not exceeding 102°F (Table 2).

Patients presenting with intermittent fever spikes may have fever following recent blood transfusions. Blood transfusions causing febrile

Table 2. CLINICAL APPROACH TO OUTBREAKS OF FEVER IN HEMODIALYSIS UNITS

Normal Serum Transaminases	Elevated Serum Transaminases
Single temperature spikes	Sustained intermittent/remittent fever pattern
Inadequate disinfection of hemodialysis machines	Hepatitis viruses
High periodic concentrations of gram-negative bacilli in dialysis water	Hepatitis B virus (HBV)
Blood transfusion	Hepatitis C virus (HCV)
Infected shunt/access site	Hepatitis D virus (HDV)
	CMV
	Legionella

reactions have a bimodal time distribution with most febrile reactions occurring within the first 72 hours, followed by a late fever reaction that occurs approximately a week after blood or blood product transfusion. The diagnosis is made by excluding other causes of fever and by relating the febrile episodes temporally to the antecedent transfusion of blood or blood products.

If the patient has not received blood or blood products, then the clinician should qualitatively and quantitatively evaluate the hemodialysis water for aerobic gram-negative bacilli. High concentrations of aerobic gram-negative bacilli (e.g., *Alcaligenes, Achromobacter, Xanthomonas, Burkholderia*, etc.), may elaborate sufficient endotoxin to pass through hemodialysis membrane and give the patient fever on the basis of endotoxinemia rather than infection.[7,38] Gram-negative aerobic bacilli present in high concentration in hemodialysis water also may cause bacteremia if they gain access to the patient's blood by way of defective dialysis filters. Patients with gram-negative bacillary bacteremia caused by the same organism that is found in high concentration in the dialysis water should prompt a search for defective or inadequate disinfection procedures of the dialysis machine between patients.[47] If hemodialysis machine disinfection procedures are adequate, then dialysis filter defects should be considered as the next possible cause of the patient's gram-negative bacillary bacteremia.[13] With a cluster of febrile reactions in a dialysis unit, dialysis water or inadequate dialysis machine disinfection should be suspected as the cause of fever.[43]

Venous shunt or access site infections should be considered in individual dialysis patients with fever. If there are signs of infection at the access site, diagnosis is obvious, but more commonly, the clinical presentation is that of few if any physical signs related to infection at the access site in patients with intermittent fevers and bacteremia. Infections involving foreign implant materials used for permanent vascular access may be caused by either gram-positive or gram-negative pathogens. Graft site infection should be considered if no other source of fever can be found in a dialysis patient.[27] Patients with infected grafts typically have intermittent bacteremias caused by the same organism, which may transiently respond to antimicrobial therapy only to repeatedly recur (Fig. 1). Graft site infections may be diagnosed by gallium or indium scans, which localizes the process to the graft or shunt site (Fig. 2). Cure of shunt-associated infections requires removal of the shunt.

Low-Grade Fevers and Increased Serum Transaminases

The other major clinical mode of presentation in patients with fever on dialysis is that of otherwise unexplained transaminase elevations with persistent low-grade fevers. Often, viral hepatitis is the cause of unexplained transaminase elevations in hemodialysis patients. Hepatitis B virus is the hepatitis virus often most associated with dialysis patients.

the influenza vaccine and the polyvalent pneumococcal vaccine has been recommended for patients with chronic renal failure. The suboptimal antibody response seen in these patients can be enhanced by reinforced vaccination, higher vaccine dosage, and adjuvant immunomodulation.[55] Dialysis therapy does not correct the defect but rather impairs the humoral antibody response.

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